REMARKS

Prior to entry of the instant amendment, claims 1, 3, 4, 19, 21, 22, 27, 33-36, 39-63 and 84-108 were pending, and claims 19, 21, 22, 27, 34-36, 40-63, 91-108 were pending and withdrawn. Claims 1, 3, 4, 33, 39, 87 and 88 have been amended. Claims 84-86 have been canceled. Accordingly, upon entry of the presently amended claim set, claims 1, 3, 4, 19, 21, 22, 27, 33-36, 39-63 and 87-108 will be pending, and claims 19, 21, 22, 27, 34-36, 40-63, 91-108 will be pending and withdrawn.

Claim 1 has been amended to correct an obvious typographical error in the word "cleavage". Claim 1 has also been amended to specify that both the sense strand and the antisense strand comprise uridines, cytidines, adenosines and guanosines, and that both strands are modified by the substitution of each uridine with a 2'-fluoro uridine and each cytidine with a 2'-fluoro cytidine, and that the antisense strand is modified by the substitution of at least one adenosine with 2'deoxy adenosine or at least one guanosine with 2'-deoxy guanosine within the 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site, such that *in vivo* stability is enhanced as compared to a corresponding unmodified siRNA, and such that the siRNA retains the ability to inhibit expression of the target mRNA by at least 30% as compared to a corresponding unmodified siRNA.

Support for this amendment can be found at least, for example, in pending claim 85, as well as the disclosure of the modified siRNA species of Figure 13D. Accordingly, claims 84 and 85 have been canceled.

Claims 3, 4, 33, 39, 87 and 88 have been amended to be dependent on claim 1. Support for these amendments can be found in claims 3, 4, 33, 39, 87 and 88, respectively.

The foregoing claim amendments have been made solely for the purpose of expediting prosecution of the present application and should in no way be construed as acquiescence to any of the Examiner's rejections in this or in any other Office Action issued in the present application. Applicant reserves the right to pursue the subject matter of the present claims prior to being amended herein in this application or in another related application.

In view of the foregoing claim amendments and the arguments set forth below, Applicant respectfully submits that the claims are now in condition for allowance.

Claims Objections

Claim 86 is objected to on the grounds that it fails to further limit the subject matter of the claim on which it depends. By way of response, Applicant notes that claim 86 has been canceled.

Claim 1 is objected to because of the misspelling of the word "cleavage". Claim 1 has been amended to correct the obvious typographical error.

Rejection of Claims Under 35 USC §112, first paragraph

Claims 1, 3-4, 33, 39 and 84-90 stand rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner alleges that the specification fails to provide adequate support for "siRNA targeted to any mRNA wherein the antisense strand comprises at least one 2'-deoxy adenosine or 2'-deoxy guanosine within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site..." and furthermore that "the breadth of the instant claims encompasses knowing the cleavage site of any target mRNA as well as the sequences of the target region..." Applicant notes that claims 84-86 have been canceled *solely to expedite prosecution*, thereby rendering the rejection moot with regard to these claims. With regard to the remaining rejected claims, Applicant respectfully traverses the rejection and takes the position that disclosure of "all known target mRNA," including the "cleavage site of all known mRNA," is not necessary in order to demonstrate that Applicant possessed the invention. As discussed in the Guidelines for Examination of Patent Applications under 35 U.S.C. 112, paragraph 1, (Fed. Reg. 66(4):1103) a determination as to whether one of skill in the art would recognize that an applicant was in possession of a claimed invention involves consideration of the following:

i) Actual reduction to practice;
ii) Disclosure of drawings or structural chemical formulas;
iii) Sufficient relevant identifying characteristics;
iv) Method of making the claimed invention;
v) Level of skill and knowledge in the art; and
vi) Predictability in the art.

In accordance with (*i*), the present application discloses actual reduction to practice in Figure 13D of the application as filed. Columns 25-60 of Figure 13D represent normalized measurements of EGFP expression in HeLa cells in the presence of four different species of

modified siRNA according to amended claim 1. The four species represent different combinations of the specific chemical modifications recited in amended claim 1, and all species retained the ability to inhibit target expression by at least 30% at a variety of concentrations.

In accordance with (*ii*), the application discloses drawings and structural representations of the claimed siRNA compounds in Figure 13C, as well as chemical formulas of the chemically-modified nucleosides of amended claim 1 in Figure 19B.

In accordance with (*iii*), sufficient relevant identifying characteristics of the claimed compounds are provided, as follows:

a) Complete structure: The complete sequences of four representative siRNA duplexes, as well as the sequence of the mRNA target region, including the precise location of the cleavage site, are depicted in Figure 13C;

b) Partial structure: The present invention involves siRNA molecules that have been chemically-modified in order to confer enhanced *in vivo* stability and simultaneously preserve the ability to promote RNAi. The conceptual starting point for designing a compound of the invention is an siRNA molecule that targets an mRNA of interest. The exact sequence of the unmodified parent siRNA will be known, and this sequence represents a *partial structure*, conversion of which to any one of a *finite* number of complete structures is accomplished as proscribed by the instant claims. The information that is needed in order to convert a partial structure to a complete structure includes the specific chemical modifications to be used, and the specific locations of the modifications. This information is disclosed in the claims, *i.e.*, the sense strand and the antisense strand are modified by the substitution of each uridine with a 2'-fluoro uridine and each cytidine with a 2'-fluoro cytidine and the antisense strand is further modified by the substitution of at least one adenosine with 2'deoxy adenosine or at least one guanosine with 2'-deoxy guanosine within the 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site.

At the time of the invention, one of skill in the art would be aware that "[t]he cleavage site on target mRNA [had] been shown to be determined by the 5' end position of the target-recognizing siRNA" (paragraph [0277], referencing Elbashir *et al.*, *EMBO J.*, Vol. 20, No. 23, 6877-6888, 2001). Moreover, the putative location of the cleavage site of the target mRNA is taught by the present application to be near the center of the complementary portion of the target RNA, and is further specified to be located about 8-12 nucleotides from the 5′ end of the

complementary portion of the target RNA. See, *e.g.*, paragraph [055]. Thus, the skilled practitioner would know the approximate location of the cleavage site of the target mRNA with no experimentation at all. Furthermore, the state of the art at the time of the invention permitted the skilled practitioner to determine the precise location of the cleavage site by treating a target with an unmodified siRNA, followed by resolution and analysis of the cleavage products. The present application teaches that this *in vitro* RNAi assay was well known in the art at the time of filing. See, *e.g.*, paragraph [0311]. An example of a target RNA cleavage assay is disclosed in the application at paragraphs [0358]-[0359].

c) Functional characteristics when coupled with disclosed correlation between function and structure: The claimed compounds are characterized, in part, by the functional characteristic that the "siRNA retains the ability to inhibit expression of the target mRNA by at least 30%." This characteristic is correlated to the specific, claimed chemical modifications.

Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP §2163 (II)(A)(3)(a); See also Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

In accordance with (*iv*), the present application discloses a method of making the claimed invention. For example, methods for selection of a target sequence are disclosed, e.g., at paragraphs [0150]-[0151]. Methods for synthesis of the claimed compounds are disclosed, e.g., at [0124]-[0126], and methods for assaying the efficacy of the claimed compounds are disclosed, e.g., at [0114]-[0123].

Finally, in accordance with (*v*) and (*vi*), the disclosures of the present application are adequate in view of the level of skill and knowledge in the art, as well as the level of predictability in the art. Specifically, at the time of filing of the present application, one of skill in the art was able to reliably and reproducibly practice the methods and techniques disclosed in the application, particularly those described in (*iv*).

The foregoing considerations support Applicants position that the claimed invention is adequately supported by the specification, and that one of skill in the art would recognize that an applicant was in possession of a claimed invention. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1, 3-4, 33, 39 and 84-90 under 35 USC §112, first paragraph.

Rejection of Claims 1, 3-4, 33, 39 and 84-90 USC §103(a)

Claims 1, 3-4, 33, 39 and 84-90 stand rejected under 35 USC §103(a) as being unpatentable over McSwiggen et al. (US2004/0192626). As a preliminary matter, Applicants note that claims 84-86 have been canceled, thereby rendering the rejection moot with respect to these claims. Applicant respectfully traverses the rejection with respect to claims 1, 3-4, 33, 39 and 87-90. However, solely to expedite prosecution, claim 1 has been amended to specify that the siRNA comprises "a sense strand and an antisense strand…wherein the sense strand and the antisense strand are modified by the substitution of each uridine with a 2'-fluoro uridine and each cytidine with a 2'-fluoro cytidine…and wherein the antisense strand is modified by the substitution of at least one adenosine with 2'deoxy adenosine or at least one guanosine with 2'-deoxy guanosine..."

McSwiggen *et al.* teaches siRNA molecules wherein one or both strands can be chemically modified. McSwiggen *et al.* discloses specific embodiments of chemically-modified siRNA, including an embodiment wherein both strands comprise 2'-fluoro pyrimidine nucleotides and 2'deoxy purine nucleotides. In contrast to the instant invention as set forth in amended claim 1, McSwiggen *et al.* do not disclose siRNA molecules wherein the antisense strand and the sense strand comprise 2'-fluoro pyrimidine nucleotides, and the antisense strand further comprises 2'deoxy purine nucleotides. As such, the cited reference fails to disclose each and every element of the claimed invention.

When determining whether a claim is obvious, an examiner must make "a searching comparison of the claimed invention - *including all its limitations* - with the teaching of the prior art." *In re Ochiai,* 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.,* 349 F.3d 1333, 1342 (Fed. Cir. 2003) *(citing In re Royka,* 490 F.2d 981, 985 (CCPA 1974)). Moreover, as the Supreme Court recently stated, "*there must be some articulated reasoning* with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added)). The failure of an asserted reference to reveal each and every feature of a claim remains fatal to an obviousness rejection under 35 U.S.C. § 103. The asserted reference must therefore embrace *each and every claim feature.* See *In re Royka,* 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (emphasis added) (to establish *prima facie* obviousness of a claimed invention, all the

claim features must be disclosed by the prior art). Indeed, as the Board of Patent Appeals and Interferences has confirmed, a proper obviousness determination requires that an examiner make "a searching comparison of the claimed invention - *including all its limitations* - with the teaching of the prior art." See *In re Wada and Murphy,* Appeal 2007-3733, citing *In re Ochiai,*71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). Further, the necessary presence of all claim features is axiomatic, since the Supreme Court has long held that obviousness is a question of law based on underlying factual inquiries, including ... ascertaining the differences between *the claimed invention* and the prior art. *Graham v. John Deere Co.,* 383 U.S. 1, 148 USPQ 459 (1966) (emphasis added). Indeed, Applicant submits that this is why Section 904 of the MPEP instructs Examiners to conduct an art search that covers "the invention *as described and claimed."* (emphasis added). In sum, it remains well-settled law that obviousness requires a teaching of all of the elements in a claim. See *In re Wada and Murphy,* citing *CFMT, Inc. v. Yieldup Intern. Corp.,*349 F.3d 1333, 1342 (Fed. Cir. 2003) and *In re Royka,* 490 F.2d 981, 985 (CCPA 1974)). Therefore, the aforementioned limitations of independent claim 1, and any dependent claim therefrom, particularly the limitations regarding differential modification of pyrimidine and purine nucleotides, and differential treatment of pyrimidine and purine nucleotides in the sense strand and the antisense strand, cannot reasonably be said to be present in the disclosure of McSwiggen *et al.* Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims under 35 USC §103(a).

Rejection of Claims Under 35 USC §112, first paragraph

Claims 1, 3-4, 33, 39 and 84-90 stand rejected under 35 USC §112, first paragraph. The Examiner alleges that one of skill in the art would not reasonably conclude that the inventor had possession of the claimed invention. Applicant respectfully disagrees, at least for the reasons set forth in the response mailed on August 12, 2009.

The instant application teaches that an siRNA molecule may be chemically-modified according to claim 1, such that *in vivo* stability is enhanced as compared to a corresponding unmodified siRNA, and such that the siRNA molecule retains the ability to inhibit expression of the target mRNA by at least 30% ***as compared to a corresponding unmodified siRNA*** (*i.e.*, the chemically-modified siRNA retains at least 30% of the activity of the corresponding unmodified siRNA). In Figure 13D, the specification describes four species of chemically-modified siRNA

compounds according to amended claim 1, each with FU/FC modifications in the sense strand and antisense strand, and differentially positioned dA/dG modifications in the antisense strand as follows:

1) antisense strand (AS) positions 9, 10 and 13;

2) AS positions 9 and 19;

3) AS positions 1-13; and

4) AS all positions

All four species of siRNA retained the ability to inhibit expression of the target gene by at least 30% ***as compared to a corresponding unmodified siRNA*** (as indicated by a coordinate of less than 0.7 on the Y axis) at a variety of concentrations (as indicated, in units of nM, on the X axis). The results of Figure 13D show that the efficacies of the chemically-modified siRNA compounds according to claim 1 are strongly correlated to the efficacy of the unmodified parent siRNA (as indicated in columns 2-6), and are not strongly correlated to the disposition of the chemical modifications within the compounds. Thus, Applicant has shown possession of the invention by demonstrating the robust effects that result from the specific chemical modifications found in the compounds of claim 1.

In addition to the results of Figure 13D, the instant application teaches that compounds of the invention can be designed to target any gene of known sequence (page 41, lines 3-18). The application teaches methods of production and purification (pages 34-35) and assays to be used to determine efficacy (pages 30-32). As such, one of skill in the art would recognize a compound of the claimed invention on the basis of the structural characteristics and functional characteristics set forth in claim 1, together with the efficacy assays taught in the specification as filed, and would reasonably conclude that Applicant was in possession of the invention at the time of filing.

In view of the foregoing, Applicants take the position that the instant claims meet the requirements for written description, and respectfully request reconsideration and withdrawal of the rejection of the claims under 35 USC §112, first paragraph.

CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If there are any questions regarding the proposed amendments to the application, we invite the Examiner to call Applicant's representative at the telephone number below.

An extension of time and appropriate fee is being filed herewith. If any additional fees are due, please charge our Deposit Account No. 12-0080, under Order No. UMY-062RCE2 from which the undersigned is authorized to draw.

Dated: November 8, 2010

Respectfully submitted,

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